				, Ç		(,
Sul	bstitute for for	m 1449A/PT	0	S TO THE WAY	Complete if Known	
				Application Number	10/611,398 (Confirmation No. 1890)	
IN	VFORMA	TION DI	ISCLOSURE	Filing Date	June 30, 2003	
S	FATEME	NT BY A	APPLICANT	First Named Inventor	PIZZA et al.	
Į.				Group Art Unit	1642	
	(use as ma	ny sneets a	s necessary)	Examiner Name	Unassigned	
Sheet	1	of	3	Attorney Docket Number	PP000338.0105 (2300-0338.02)	

	U.S. PATENT DOCUMENTS									
		U.S. Patent	Document		Date of Bublication of Cited					
Examiner Initials*	Cite Number Kind Code ² Name of Patentee or Applicant of Cited Document No. ¹ (if known)	Date of Publication of Cited Document MM-DD-YYYY								
1/	'A1	5,182,109		Tamura, et al.	01-26-1993					
<i>T</i>										
		-								
-		· · · · · · · · · · · · · · · · · · ·		· · · · · · · · · · · · · · · · · · ·	***************************************					

		•		FOREIGN	PATENT DOCUMENTS			
Examiner Initials*	Cite	Cite No.		Foreign Patent Doo	ument		Date of Publication	T
	Initials No.		Office ³ Number ⁴		Name of Patentee or Applicant of Cited Document	of Cited Document MM-DD-YYYY	. T€	
-71	Bl	·wo	95/09649	The state of the s	MEDEVA HOLDINGS B.V.	04-13-1995		
ן ט	B2	wo	95/34323		CONNAUGHT LABORATORIES LIMITED	12-21-1995		
	B3	wo	96/06627		THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND	03-07-1996		
	B4	wo	99/58145		UNIVERSITY OF BRISTOL	11-18-1999		
I	B5	wo	00/18434		AMERICAN CYNAMID COMPANY	04-06-2000	<u> </u>	
	B6	EP	0396964		SCLAVO S.P.A.	11-14-1990		
1	B7	EP	0462534		SCLAVO S.P.A.	12-27-1991		
	B8	GB	9320454.3		MEDEVA HOLDINGS B.V			
	B9	GB	9324743.5		MEDEVA HOLDINGS B.V			
						·		
		├						
		├						
	1	1 1					ł	

				\sim	&
Examiner		Date		9 1 7	1 7
Signature		Considered	[2]	IIU	, .
*EXAMINER:	Initial if reference considered, w	hether or not citation is in conformance with MPI	EP 609. Draw line th	rough cit	ation if not in conformance

and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number.

² See attached Kinds of U.S. Patent Documents.

¹ Unique citation designation number.

² See attached Kinds of U.S. Patent Documents.

For attached Kinds of U.S. Patent Documents.

Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

Skind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08A (08-00)

Su	bstitute for fo	orm 1449A/PT	·o		Complete if Known
	· ·			Application Number	10/611,398 (Confirmation No. 1890)
II.	NFORM A	ATION D	ISCLOSURE	Filing Date	June 30, 2003
· S'	TATEM	ENT BY A	APPLICANT	First Named Inventor	PIZZA et al.
	,			Group Art Unit	1642
	(use as n	any sheets a	s necessary)	Examiner Name	Unassigned
Sheet	2	of	3	Attorney Docket Number	PP00338.105 (2300-0338.02)

		OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS
Examiner Initials*	Cite No.'	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
XI	Cl	Burnette, "The Advent of Recombinant Pertussis Vaccines." Biotechnol. 8:1002-1005 (1990)
-//	C2	Burnette, Vaccine Research & Developments Marcel Dekker Inc., New York, New York (1992)
	C3	Clements, et al., "Adjuvant Activity of Escherichia Coli Heat-Labile Enterotoxin and Effect on the Induction of Oral Tolerance in Mice to Unrelated Protein Antigens." Vaccine 6:269-277 (1988)
	C4	Communication to EPO Concerning Replacement Claims for Filing with the EPO in Application No. 99922284.7 (2003)
	C5	de Haan, et al., "Mutational Analysis of the Role of ADP-Ribosylation Activity in the Adjuvant Properties of the Escherichia Coli Heat-Labile Enterotoxin Towards Intranasally Administered Keyhole Limpet Hemocyanin." Eur. J. Immunol. 28:1243-1250 (1998)
	C6	Del Guidice, et al., "Genetically Derived Toxoids for use as Vaccines and Adjuvants." Vaccine 17:S44-S52 (1999)
	C7	Douce, et al.,"Mutants of Escherichia Coli Heat-Labile Toxin Lacking ADP-Ribosyltransferase Activity act as Nontoxic, Mucosal Adjuvants." PNAS USA 92:1644-1648 (1995)
	C8	Douce, et al., "Intranasal Immunogenicity and Adjuvanticity of Site Directed Mutant Derivatives of Cholera Toxin." Infect. Immun. 65:2821-2828 (1997)
	C9	EPO Communication pursuant to Article 96(2) EPC relating to Application EP No. 94928455.8-2116 (2001)
	C10	"Multicomponent Vaccine Development." NIH Guide Volume 22, Number 28 (1993)
	CH	Green, Bruce, Curriculum Vitae
	C12	Hagen, Michael, Curriculum Vitae
	C13	Hagiwar, et al., Effectiveness and Safety of Mutant Escherichia Coli Heat-Labile Enterotoxin (LT H44A) as an Adjuvant for Nasal Influenza Vaccine." Vaccine 19:2071-2079 (2001)
	C14	Hartman, et al., "Native and Mutant Forms of Cholera Toxin and Heat-Labile Enterotoxin Effectively Enhance Protective Efficacy of Live Attenuated and Heat-Killed Shigella Vaccines." Infect. Immun. 67:5841-5847 (1999)
	CIS	Hazama, et al., "Intranasal Immunization Against Herpes Simplex Virus Infection by using a Recombinant Glycoprotein D Fused with Immunomodulating Proteins, the B Subunit of Escherichia Coli Heat-Labile Enterotoxin and Interleukin-2." Immunology 78:643-649 (1993)
	CI6	Hirst, et al., "Cholera Toxin and Related Enterotoxins as Potent Immune Modulators." J. Appl. Microb. Symp. Suppl. 48:26S-34S (1998)
	C17	Hirst, The Comprehensive Sourcebook of Bacterial Protein Toxins, Chapter 6, Academic Press, pgs. 104-130, (1999)
	C18	Holmgren, et al., "Cholera Toxin and Cholera B Subunit as Oral-Mucosal Adjuvant and Antigen Vector Systems." Vaccine 11:1179-1184 (1993)
	C19	Lycke, et al., "Strong Adjuvant Properties of Cholera Toxin on Gut Mucosal Immune Responses to Orally Presented Antigens." Immunol. 56:301-308 (1986)
	C20	Lycke, et al, "The Mechanism of Cholera Toxin Adjuvanticity." Res. Immunol. 198:504-520 (1997)
	C21	Martindale, Royal Pharmaceutical Society of Britain Pharmaceutical Press, London, England, pgs.1277-1304(1993)
	C22	Rappouli, et al., "Structure and Mucosal Adjuventicity of Cholera and Escherichia Coli Heat-Labile Enterotoxins." Immunol. Today 20:493-500 (1999)
	C23	Spangler, "Structure and Function of Cholera Toxin and The Related Escherichia Coli Heat-Labile Enterotoxin." Microbiol. Rev. 56:622-647 (1992)
	C24	Streatfield, et al., "Intermolecular Interactions Between the A and B Subunits of Heat-Labile Enterotoxin from Escherichia Coli Promote Holotoxin Assembly and Stability In Vivo." PNAS USA 89:12140-12144 (1992)
	_C25	The Comprehensive Sourcebook of Bacterial Protein Toxins, 2 nd Ed., Academic Press, pgs. 696-697
	C26	Tsuji, et al., "Relationship Between a Low Toxicity of the Mutant A Subunit of Enterotoxigenic Escherichia Coli Enterotoxin and its Strong Adjuvant Action." Immunology 90:176-182 (1997)

		 	=		~	
Examiner	\sim / \sim	Date		1,01	<u> </u>)
Signature	(γ '	Considered		1111	O'I	/
PEVAMBLED.	Internal Conference Co	 		- 		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PTO/SB/08A (08-00)

Sul	stitute for f	form 1449A/P1	го		Complete if Known	
				Application Number 10/611,398 (Confirmation No. 1890)		
IN	INFORMATION DISCLOSURE			Filing Date	June 30, 2003	
S	TATEM	ENT BY	APPLICANT	First Named Inventor	PIZZA et al.	
				Group Art Unit	1642	
	(use as I	nany sheets o	is necessary)	Examiner Name	Unassigned	
Sheet	3	of	3	Attorney Docket Number	PP00338.105 (2300-0338.02)	

		OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS
Examiner	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
	C27	Verweij, et al., Mucosal Immunoadjuvant Activity of Recombinant Escherichia Coli Heat-Labile Enterotoxin and its B Subunit: Induction of Systematic IgG and Secretory IgA Responses in Mice by Intranasal Immunization with Influenza Virus Surface Antigen." Vaccine 16:2069-2076 (1998)
	C28	Walker, et al., "Use of Heat-Labile Toxin Enterotoxigenic Escherichia Coli to Facilitate Mucosal Immunization." Vaccine Res. 2:1-10 (1993)
	C29	Williams, Neil, Affidavit, Curriculum Vitae, and Annex 1
	C30	Yamamoto, et al., "Mutants in the ADP-Ribosyltransferase Cleft of Cholera Toxin Lack Diarrheagenicity but Retain Adjuvanticity." J. Exp. Med. 185:1203-1210 (1997)
	<u> </u>	
		
		
	 	
	 	
	·	
	1	
İ		
		·
	— —	
	-	
	 	
 	 	
	 	
	 	
T	1	

Examiner Signature		Date - Considered		19/0	<i>t</i>
	idered, whether or not citation in the citation of the communication of the citation of the ci	on is in conformance with Mation to applicant.	IPEP 609. Draw lin	through citation	if not in conformance

MAR 1 9 7074 F

Complete if Known Substitute for form 1449A/PTO **Application Number** 10/611,398 (Confirmation No. 1890) INFORMATION DISCLOSURE Filing Date June 30, 2003 PIZZA et al. STATEMENT BY APPLICANT First Named Inventor Group Art Unit 1642 (use as many sheets as necessary) Examiner Name Unassigned Sheet of Attorney Docket Number PP00338.105 (2300-0338.02)

	U.S. PATENT DOCUMENTS										
		U.S. Patent Document			Day of Day of Color						
Examiner Initials	Cite No.1	Number	Kind Code ¹ (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY						
1	Al	4,328,209		Finkelstein et al.	5/4/82						
	A2	4,666,837		Harford et al.	5/19/87						
T	A3	4,935,364		Kaper et al.	6/19/90						
	A4	5,601,827		Collier et al.	2/11/97						
	A5	5,668,255		Murphy .	9/16/97						
	A6	5,770,203		Burnette et al.	6/23/98						
	A7	6,019,982		Clements et al.	2/1/00						
	A8	6,033,673		Clements	3/7/00						
	A9	6,149,919		Domenighini et al.	11/00						

	V			FOREIGN	PATENT DOCUMENTS		
Examiner Initials*	Cite	roleign ratent Document				Date of Publication	
	No.'	Office	3 Number ⁴	Kind Code ⁵ (if known)	Name of Patentee or Applicant of Cited Document	of Cited Document MM-DD-YYYY	τ⁵
CXI	Bl	wo	92/19265			11/12/92	
3	B2	wo	93/13202		Domenighini	7/8/93	
	ļ	ļ					
	l					-	

Examiner	0/20=	Date	196	
Signature		Considered		

^{*}EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Unique citation designation number.

² See attached Kinds of U.S. Patent Documents.

¹ Unique citation designation number.

² See attached Kinds of U.S. Patent Documents.

³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible.

⁶ Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449A/PTO			0	Complete if Known		
				Application Number	10/611,398 (Confirmation No. 1890)	
II	INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)			Filing Date	June 30, 2003	
S				First Named Inventor	PIZZA et al.	
				Group Art Unit	1642	
				Examiner Name	Unassigned	
Sheet	2	of	3	Attorney Docket Number	PP00338.105 (2300-0338.02)	

		OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.
И	Ci	BOSLEGO, J.W. et al., Vaccines and Immunotherapy, Chapter 17, 1991, 211-223
0	C2	BURNETTE, W.N. et al., "Site-specific mutagenesis of the catalytic subunit of cholera toxin: substituting lysine for arginine 7 causes loss of activity," Inf. & Immun., 1991, 59:4266-4270
	C3	DALLAS, W.S. et al., "Cistrons encoding Escherichia coli heat-labile toxin," J. Bacteriol., 1979, 139:850-858
	C4	DENTE, L. et al., "pEMBL: a new family of single stranded plasmids," Nucleic Acids Res., 1983 11(6):1645-1655
	C5	DOMENIGHINI, M. et al., "Identification of errors among database sequence entries and comparison of correct amino acid sequences for the heat-labile enterotoxins of Eschericia coli and Vibrio cholerae," Mol. Microbiol., 1995, 15(6):1165-1167
	C6	DOMENIGHINI, M. et al., "Common features of the DNA-binding and catalytic site of ADP-ribosylating toxins," Mol. Microbiol., 1994, 14(1):41-50
	C7	DICKINSON, B. et al., "Dissociation of Escherichia coli heat-labile enterotoxin adjuvanticity from ADP-ribosyltransferase activity," Infection and Immunity, 1995, 63(5):1617-1623
	C8	DONTA, S., "Detection of heat-labile Escherichia coli enterotoxin with the use of adrenal cells in tissue culture," Science, 1974, 183:334-336
	C9 .	FONTANA, M.R. et al., "Construction of nontoxic derivatives of cholera toxin and characterization of the immunological response against the A subunit," Infection and Immunity, 1995, 63(6):2356-2360
	C10	GRANT, C. et al., "Role of trypsin-like cleavage at arginine 192 in the enzymatic and cytotonic activities of Escherichia coli heat-labile enterotoxin," Infection and Immunity, 1994, 62(10):4270-4278
	CH	GRANT, C.C.R. et al., "Effect of single amino acid changes on the ADP-ribosyltransferase activity of Escherichia coli heat-labile toxin subunit A," 92 rd Gen. Meet. Am. Soc. Microbiol., 1992, Abstract B278, 74
	C12	HARFORD, S. et al., "Inactivation of the Escherichia coli heat-labile enterotoxin by in vitro mutagenesis of the A-subunit gene," Eur. J. Biochem., 1989, 183:311-316
	C13	HASE, C. et al., "Construction and characterization of recombinant Vibrio cholerae strains producing inactive cholera toxin analogs," Infection and Immunity, 1994, 62(8):3051-3057
	C14	HIRST, T. et al., "Transient entry of enterotoxin subunits into the periplasm occurs during their secretion from Vibrio cholerae," J. Bacteriol., 1987, 169(3):1037-1045
	C15	HOLMGREN, J. et al., "Oral immunization against cholera," Curr. Top. Microbiol. Immunol., 1998, 146:197-204
	C16	JOBLING, M.G. et al., "Analysis of the structure and function of cholera toxin A subunit," Abstr. Gen. Meet. Am. Soc. Microbiol., 1991, 91(0), 59, #B205
	C17	KASLOW, H.R. et al., "Effects of site-directed mutagenesis on cholera toxin A1 subunit ADP-ribosyltransferase activity," 92 nd Gen. Meet. Am. Soc. Microbiol., 1992, Asbract B291, 74
	C18	KASLOW, H.R. et al., "Site-specific mutagenesis of the pertussis toxin S1 subunit gene: effects of amino acid substitutions involving residues 50-58," Vaccine Research, 1992, 1(1):47-54
	C19	LAI, C.Y. et al., "Location and amino acid sequence around the ADP-ribosylation site in the cholera toxin active subunit A ₁ ," Biochem. Biophys. Res. Comm., 1983, 116:341-348
_	C20	The Lancet, September 27, 1986, 328(8509):722-723, "Oral Cholera Vaccines"
	C21	LEBACQ-VERHEYDEN, A.M. et al., "Posttranslation processing of endogenous and of baculovirus-expressed human gastrin- releasing peptide precursor," Mol. Cell. Biol., 1988, 8:3129-3135
	C22	LOBET, Y. et al., "Effect of site-directed mutagenic alterations on ADP-ribosyltransferase activity of the A subunit of Escherichia coli heat-labile enterotoxin," Inf. & Immun., 1991, 59:2870-2879
.]	C23	LOOSEMORE, S.M. et al., "Engineering of genetically detoxified pertussis toxin analogs for development of a recombianant whooping cough vaccine," Infection and Immunity, 1990, 58(11):3653-3662
	C24	LYCKE, N. et al., "The adjuvant effect of Vibrio cholerae and Escherichia coli heat-labile enterotoxins is linked to their ADP-ribosyltransferase activity," Eur. J. Immunol., 1992, 22:2277-2281

Examiner		Date	<i>r</i> 1		7
Signature		Considered	(0)	19/1	
OFYAMINED.	Initial if reference considered whether as not airction is in-			advision in	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PTO/SB/08A (08-00)

Su	Substitute for form 1449A/PTO			Complete if Known		
				Application Number	10/611,398 (Confirmation No. 1890)	
INFORMATION DISCLOSURE		Filing Date	June 30, 2003			
S	STATEMENT BY APPLICANT		First Named Inventor	PIZZA et al.		
				Group Art Unit	1642	
	(use as many sheets as necessary)		Examiner Name	Unassigned		
Sheet	3	of	3 ·	Attorney Docket Number	PP00338.105 (2300-0338.02)	

	C25	MAGAGNOLI, C. et al., "Mutations in the A subunit affect yield, stability, and protease sensitivity of nontoxic derivatives of heat-labile enteroxotin," Infection and Immunity, 1996, 64(12):5434-5438
A	C26	MEKALANOS, J.J. et al., "Cholera toxin genes: nucleotide sequence, deletion analysis and vaccine development," Nature, 1983, 306:551-557
	C27	Molecular Microbiology, 1995, 15(6):1165-1167, "MicroCorrespondence"
	C28	OKAMOTO, J. et al., "Effect of substitution of glycine for arginine at position 146 of the A1 subunit on biological activity of Escherichia coli heat-labile enterotoxin," Bacteriol., 1988, 2208
	C29	OSEASOHN, R., "Cholera," In Plotkin S.A., Mortimer, E.A. (Eds.), Vaccines, 1988, WB Saunders Co., Philadelphia, PA
	C30	PEARSON, G. et al., "Molecular cloning of Vibrio cholerae enterotoxin genes in Escherichia coli K-12," Proc. Natl. Acad. Sci. USA, 1982, 79:2976-2980
	C31	PICKETT, C.L. et al., "Genetics of type lia heat-labile enterotoxin of <i>Escherichia coli</i> : operon fusions, nucleotide Sequence, and hybridization studies," <i>J. Bacteriol.</i> , 1987, 169:5180-5187
	C32	PIZZA, M. et al., "A genetically detoxified derivative of heat-labile Escherichia coli enterotoxin induces neutralizing antibodies against the A subunit," J. Exp. Med., 1994, 180:2147-2153
	C33	PIZZA, M. et al., "Probing the structure-activity relationship of Escherichia coli LT-A by site-directed mutagenesis," Mol. Microbiol., 1994, 14(1):51-60
	C34	PIZZA, M. et al., "The subunit S1 is important for pertussis toxin secretion," J. Biol. Chem., 1990, 265(29):17759-17763
	C35	PRONK, S. et al., "Heat-labile enteroxotin of Escherichia coli," J. Biol. Chem., 1985, 260(25):13580-13584
	C36	RAPPUOLI, R. et al., "Structure and evolutionary aspects of ADP-ribosylating toxins, Sourcebook of Bacterial Toxins, 1991, Academic Press Limited, 1-21
	C37	SANDKVIST, M. et al., "Assembly of Escherichia coli heat-labile enterotoxin and its secretion from Vibrio cholerae," Molecular Meachanisms of Bacterial Virulence, 1993, Chapter 21, 293-309
	C38	SIXMA, T.K. et al., "Crystal structure of a cholera toxin-related heat-labile enterotoxin from E. coli," Nature, 1991, 351:371-377
	C39	SPICER et al., "Sequence homologies between A subunits of Escherichia coli and Vibrio cholerae enterotoxins," Proc. Natl. Acac. Sci. USA, 1981, 78(1):50-54
	C40	SPICER et al., "Escherichia coli heat-labile enterotoxin," Biol. Chem., 1982, 257:5716-5721
	C41	TSUJI, T. et al., "A simple amino acid substitution in the A subunit of Escherichia coli enterotoxin results in a loss of its toxic activity," J. Biol. Chem., 1990, 265:22520-22525
	C42	YAMAMOTO, T. et al., "Primary structure of heat-labile enterotoxin produced by Escherichia coli pathogenic for humans," J. Biol. Chem., 1984, 259:5037-5044
	C43	ZOLLER, M. et al., "Oligonucleotide-directed mutagensis using M13-derived vectors: an efficient and general procedure for the production of point mutations in any fragment of DNA," Nucleic Acids Res., 1982, 10(20):6487-6500

Examiner	517	Date	1 10 0
			$(a \mid 1910)$
Signature	1/ /)	Considered	0 1 0 1 9
*EXAMINER: Ini	tial if reference considered whe	ther or not citation is in conformance with MPEP	600 Draw line through citation if not in conformance

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.